



Acne Agents, Topical Therapeutic Class Review (TCR)

January 27, 2017

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Columbia, Maryland 21046

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January 2017

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FDA-APPROVED INDICATIONS

All products included in this review are indicated for the topical treatment of acne vulgaris. Tazarotene (Tazorac) is additionally indicated for the treatment of plaque psoriasis. Sodium sulfacetamide/sulfur (Avar, Avar E, Avar E-LS, Avar LS, BP 10-1, BP Cleansing Wash, Plexion, Rosanil, SSS 10-5, SulfaCleanse, Sumadan, Sumadan XLT, Sumaxin, Zencia) is additionally indicated for topical control of acne rosacea and seborrheic dermatitis. Sodium sulfacetamide (Ovace, Ovace Plus, Ovace Plus Wash) is indicated for seborrheic dermatitis and seborrhea sicca, in addition to treatment of secondary bacterial infections of the skin due to organisms susceptible to sulfonamides.

Drug	Manufacturer
adapalene (Rx and OTC) (Differin®) ¹	generic Galderma
adapalene/benzoyl peroxide (Epiduo®, Epiduo® Forte) ^{2,3}	Galderma
azelaic acid (Azelex®) ⁴	Allergan
benzoyl peroxide (AcneFree®) ⁵ (AcneFree® Severe) ⁶ (Acne Medication) ⁷ (Acne Spot Treatment) ⁸ (Advanced Acne Wash) ⁹ (BenzeFoam™) ¹⁰ (BenzeFoam Ultra™) ¹¹ (BenzePro™) ¹² (BP) ¹³ (BP Foam) ¹⁴ (BP Foaming Wash) ¹⁵ (BP Gel) ¹⁶ (BPO) ¹⁷ (BPO-5) ¹⁸ (BPO-10) ¹⁹ (BP Wash™) ²⁰ (Dual Action Cleanser) (Effaclar Duo) (Inova™) ²¹ (OC8) ²² (Pacnex®) ²³ (Pacnex® HP) ²⁴ (Pacnex® LP) ²⁵ (Panoxyl®) (Panoxyl-4®) (Persa-Gel) ²⁶ (Riax) ²⁷	generic Valeant Valeant Rugby CVS Elorac Encore Dermatology Encore Dermatology PruGen Cintex Cintex Acella Laydan Acella Trimarc Trimarc Cintex CVS L'Oreal U.S.A. Innocutis Ferndale Medimetriks Medimetriks Medimetriks GSK Consumer HE/Steifel GSK Consumer HE J&J Consumer Products Artesa Labs

FDA-Approved Indications (continued)

Drug	Manufacturer
benzoyl peroxide/clindamycin (Acanya™) ²⁸ (BenzaClin®) ²⁹ (Duac®) ³⁰ (Neuac™) ³¹ (Onexton) ³²	Generic Valeant Valeant Stiefel Medimetriks Valeant
benzoyl peroxide/erythromycin (Benzamycin®) ³³ (Benzamycin® Pak) ³⁴	generic Valeant Valeant
benzoyl peroxide/hydrocortisone (Vanoxide-HC) ³⁵	Summers
benzoyl peroxide/salicylic acid (Inova™ 4/1, 8/2) ³⁶	Innocus
benzoyl peroxide/sulfur (NuOx) ³⁷	Generic Gentex
clindamycin (Cleocin T®) (Clindacin P) ³⁸ (Clindacin PAC™) ³⁹ (Clindacin® ETZ) ⁴⁰ (Clindagel®) ⁴¹ (Evoclin™) ⁴²	generic Pharmacia/Upjohn Medimetriks Medimetriks Medimetriks Galderma/Valeant Prestium/Mylan
dapsone (Aczone™) ⁴³	Allergan
erythromycin (Erygel) ⁴⁴ (Ery) ⁴⁵	generic Prestium Perrigo
salicylic acid (Acne Control Cleansing) ⁴⁶ (Acne Cream) ⁴⁷ (Acne Pads) ⁴⁸ (Acne Treatment) ⁴⁹ (Advanced Acne Spot Treatment) ⁵⁰ (Cleansing Pads) ⁵¹ (Clearasil Daily Clear) ⁵² (Oil-Free Acne Wash) ⁵³ (Rapid Clear) ⁵⁴	 CVS CVS Rite Aid Corp/Walgreens McKesson/Rite Aid Corp CVS Chain Drug Cons Reckitt Equaline Vitamin/Neutrogena Corp Neutrogena Corp
sodium sulfacetamide (Klaron®) ⁵⁵ (Ovace®) ⁵⁶ (Ovace® Plus) ^{57,58,59} (Ovace® Plus Wash®) ⁶⁰	Generic Valeant Mission Mission Mission

FDA-Approved Indications (continued)

Drug	Manufacturer
sodium sulfacetamide/sulfur (Avar®) ^{61,62} (Avar® E) ⁶³ (Avar® E-LS) ⁶⁴ (Avar LS™) ⁶⁵ (BP 10-1) ⁶⁶ (BP Cleansing Wash) ⁶⁷ (Plexion®) ⁶⁸ (Rosanil) ⁶⁹ (Rosula™) ⁷⁰ (SSS 10-5) ⁷¹ (SulfaCleanse) ⁷² (Sumadan™) ⁷³ (Sumadan XLT®) ⁷⁴ (Sumaxin®) ⁷⁵ (Sumaxin CP) ⁷⁶ (Sumaxin TS) ⁷⁷ (Zencia) ⁷⁸	generic Mission Mission Mission Mission Acella Acella Brava/Mission Galderma Avion Acella Prugen Medimetrics Medimetrics Medimetrics Medimetrics Medimetrics Stratus
tazarotene (Fabior™) ⁷⁹ (Tazorac®) ^{80,81}	Stiefel/Mayne Allergan
tretinoin (Atralin™) ⁸² (Avita®) ⁸³ (Retin-A®) ⁸⁴ (Retin-A Micro®) ⁸⁵ (Tretin-X™)	generic Valeant Mylan Valeant Valeant Onset Dermatology
clindamycin/tretinoin (Ziana™) ⁸⁶ (Veltin™) ⁸⁷	generic Valeant Stiefel/ Aqua Pharmaceuticals

OTC = over-the-counter; Rx = prescription required

Benzodox 30 kit and Benzodox 60 kit are not included in this therapeutic class review; these products contain doxycycline capsules and 4.4% benzoyl peroxide advanced cream/wash.

OVERVIEW

Acne vulgaris is the most common cutaneous condition in the United States. It is a disorder that affects primarily teenagers and young adults, but it can sometimes persist beyond young adulthood. In adolescence, sebaceous glands increase sebum release after puberty. Small cysts called comedones form in hair follicles due to blockage of the pore from accumulated sebum and keratinous material. Bacteria, most often *Propionibacterium acnes*, release free fatty acids from sebum within the comedones, which causes inflammation to form a cyst. This results in rupture of the cyst wall and subsequent inflammatory reaction due to extrusion of oily and keratinous debris from the cyst.

Classification of the severity of acne is not standardized in the published medical literature.⁸⁸ One method of classification is to evaluate the number and type of lesions. There are 3 categories of the severity of acne and includes either acne occurring on the face or the trunk of the body. These categories are graded as mild, moderate, or severe depending on the presence and number of lesions, which consist of comedones, papules, pustules, and/or cysts. Mild acne is defined by the presence of fewer than 20 comedones, fewer than 15 inflamed papules, or fewer than 30 lesions consisting of the combination comedones and papules. Moderate acne is defined by the presence of 15 to 50 papules and pustules in addition to comedones and rare cysts, and the total number of lesions on the face can range from 30 to 125. Severe acne is defined by the presence of mostly inflamed nodules and cysts and includes more than 125 lesions consisting of comedones, papules, and pustules.

The goals of treatment include resolution of lesions, scar prevention, and reduction of psychological morbidities.⁸⁹ This is achieved by decreasing sebaceous gland activity, bacterial population, and inflammation. The available products work by different mechanisms to attack the causative events. Typically, retinoids, such as tretinoin (Atralin, Retin-A Micro), adapalene (Differin), and tazarotene (Tazorac), are used to inhibit comedone formation, while an antibiotic, such as clindamycin or erythromycin, suppresses *P. acnes*. Combination therapy is useful to limit growing resistance to antibacterial therapy, as well as enhance the efficacy of antibiotics by improving penetration into the lesions.^{90,91,92} Since 1990, prescribing has trended more toward agents not reliant on antibacterial mechanisms.⁹³

In May 2013, the American Acne and Rosacea Society developed the first detailed, evidence-based clinical guidelines for the management of pediatric acne including issues of special concern when treating pediatric patients.⁹⁴ The guidelines recommended topical benzoyl peroxide, a topical retinoid, or topical combination therapy that includes benzoyl peroxide plus an antibiotic, with or without a retinoid, for initial treatment of mild to moderate pediatric acne. Additional treatment considerations listed within the guidelines are oral antibiotics, hormonal therapy, and isotretinoin. The treatment algorithms include therapy for adolescent, pre-adolescent, infantile, and neonatal acne and consider psychosocial effects on acne, adherence to treatment, and the effects of diet on acne.

The May 2016 American Academy of Dermatology (AAD) guidelines recommend benzoyl peroxide or combinations with erythromycin or clindamycin for mild acne or in conjunction with a topical retinoid or systemic antibiotic for moderate to severe acne.⁹⁵ They note that benzoyl peroxide is effective to prevent bacterial resistance, but topical erythromycin and clindamycin as monotherapy are not recommended due to resistance. Topical dapsone 5% gel is recommended for inflammatory acne, particularly in female adults, while azelaic acid is beneficial as an adjunctive treatment for patients with postinflammatory dyspigmentation. For preadolescent acne in children, topical adapalene, tretinoin, and benzoyl peroxide are recommended. The guidelines state topical retinoids play a key role in monotherapy for comedonal acne or as combination therapy with other topical or oral antimicrobials for patients with mixed or primarily inflammatory acne lesions. The guidelines recommend combination therapy with agents with different mechanisms to target acne pathogenesis in the majority of patients. They also state that evidence of sulfur, nicotinamide, resorcinol, sodium sulfacetamide, aluminum chloride, and zinc use for acne treatment is limited. The guidelines also note that emerging data suggest a link between a patients' diet and acne development. A high glycemic diet or milk intake, specifically skim milk, may lead to acne. Specific dietary changes are not recommended at this time given the limited data.

According to the 2009 update to the consensus guidelines developed by the Global Alliance to Improve Outcomes in Acne, the topical retinoids should be the foundation of treatment in most patients with acne as they target the microcomedone, the precursor to all acne lesions.⁹⁶ When used from the beginning of therapy, retinoids significantly increase the speed of resolution of acne lesions. For inflammatory lesions, an antimicrobial agent (e.g., benzoyl peroxide) or antibiotic can be added for synergy and faster clearing. Fixed-dose combination products improve patient convenience and potentially adherence. However, combination therapy can also increase the incidence and severity of adverse effects. Prolonged use of antibiotics for acne, both oral and topical, can increase selective pressures on microbial flora, not just *P. acnes*. This prolonged antibiotic use can also lead to the development of resistant staphylococci. Therefore, a limited duration of antibiotics is recommended. The Alliance also advises against antibacterial monotherapy due to the concern for development of bacterial resistance. Retinoid therapy with or without benzoyl peroxide should be continued as maintenance therapy upon resolution of inflammatory lesions. Antibiotic/benzoyl peroxide combinations are not ideal for maintenance therapy.

Benzoyl peroxide has bactericidal, keratolytic, and comedolytic activity and has been useful as a single agent and in combination with antibiotics or retinoids in decreasing the number of lesions in mild to moderate acne.⁹⁷ Combining a topical antibiotic with benzoyl peroxide increases efficacy, is less irritating, and reduces the development of resistant strains of *P. acnes*.^{98,99,100,101} However, since the potential for resistance still exists, the antibiotic should be discontinued as soon as inflammatory lesions begin to resolve.¹⁰² There are many different strengths and formulations available for benzoyl peroxide. It is unknown if there is increased efficacy from higher or lower concentrations of the products, but the incidence of adverse effects may increase with greater concentration of drug.

Clindamycin has been associated with greater incidences of adverse effects when introduced into the systemic circulation compared to erythromycin, but the topical application of these products allows for minimal systemic absorption. There does not appear to be any significant differences in the efficacy of these topical antibiotics. As stated above, monotherapy with these topical antibiotics is not recommended due to the development of bacterial resistance.^{103,104}

Azelaic acid (Azelex) exhibits comedolytic and antibacterial properties; it is not viewed as initial therapy.¹⁰⁵ Investigation of clinical efficacy for sodium sulfacetamide is lacking, as are the effects of combinations with sulfur. Sulfur is an older therapeutic agent that exhibits antimicrobial and keratolytic activity and has demonstrated some usefulness in the treatment of acne.^{106,107} The clinical evidence, however, demonstrating the efficacy of sulfur in acne treatment has not been consistently or reliably proven. Dapsone (Aczone) is a topical sulfone developed from the oral formulation which is used to treat leprosy.¹⁰⁸ Adapalene and tazarotene have been shown to be at least as effective as tretinoin, often with a lower incidence of adverse effects.¹⁰⁹ However, tazarotene gel may be more irritating than tretinoin or adapalene. The tazarotene cream and foam formulations may be better tolerated, but how it compares in effectiveness with adapalene or tretinoin remains to be determined.

Systemic treatment is generally required in cases of severe acne, and hormonal therapy is available for females. This review focuses on the available topical preparations for acne treatment.

In 2016, the FDA approved Differin 0.1% gel (adapalene) for the treatment of acne without a prescription.¹¹⁰ The FDA noted that usage and exposure were key review issues in evaluating the potential risks of marketing for over-the-counter (OTC) use. They state that data suggests that larger package size may lead to increased usage, while limiting package size may reduce overconsumption.

PHARMACOLOGY¹¹¹

Clindamycin and erythromycin are antibiotics that inhibit bacterial protein synthesis at the ribosomal level by binding to the 50S ribosome and affecting the process of peptide chain initiation. They have been shown to have *in vitro* activity against *P. acnes*, an organism commonly associated with acne vulgaris. Antagonism has been reported between clindamycin and erythromycin. Sulfonamides such as sodium sulfacetamide (Avar, Avar E, Avar E-LS, Avar LS, BP 10-1, BP Cleansing Wash, Klaron, Ovace, Ovace Plus, Plexion, Rosanil, Rosula, SSS-10-5, SulfaCleanse, Sumadan, Sumadan XLT, Sumaxin, Zencia) probably work by acting as a competitive inhibitor of para-aminobenzoic acid utilization (PABA). PABA is an essential component for bacterial growth.

Benzoyl peroxide has a keratolytic and desquamative effect that may contribute to its efficacy. Benzoyl peroxide is bactericidal with activity against *P. acnes*, which is believed to be due to its oxidizing properties. It is available in combination with other agents, such as antibiotics and sulfur, which contributes a mild keratolytic action. Salicylic acid causes desquamation of hyperkeratotic epithelium.

The exact mechanism of action of azelaic acid (Azelex) is not known. It has been shown to have antibacterial activity against *P. acnes* and *Staphylococcus epidermidis*, as well as a normalization of keratinization that leads to an anticomedonal effect.

The exact mechanism of action of dapsone (Aczone) in the treatment of acne vulgaris is unknown, but *in vitro* studies suggest that it may suppress neutrophil recruitment oxidation, which may help prevent the production of toxic respiratory and secretory products. It may also have antimicrobial activity.

Tazarotene (Tazorac, Fabior) is a retinoid prodrug that, when activated, has antihyperproliferative, differentiation normalizing, and anti-inflammatory effects. The exact mechanism of action is unknown. Tretinoin (Atralin, Avita, Retin-A, Retin-A Micro, Tretin-X), another retinoid, works by decreasing cohesiveness of follicular epithelial cells and decreasing microcomedone formation. It may also stimulate mitotic activity and increase turnover of follicular epithelial cells, causing extrusion of the comedones.

Adapalene (Differin, Epiduo, Epiduo Forte) is a modulator of cellular differentiation, keratinization, and inflammatory processes. Although the exact mechanism of action is unknown, adapalene may normalize the differentiation of follicular epithelial cells, resulting in decreased microcomedone formation.

PHARMACOKINETICS^{112,113,114,115,116,117,118,119,120,121,122,123,124,125,126,127,128,129,130,131,132,133,134,135,136,137,138,139,140,141,142,143,144,145,146,147,148,149,150,151,152,153,154,155}

Topically-administered clindamycin has some systemic absorption and is only 1% available systemically. The low levels seen in the plasma are excreted unchanged in the urine.

Topically-administered erythromycin is not detectable in the plasma.

Less than 2% of benzoyl peroxide is absorbed in the systemic circulation. Due to the lipophilic nature, benzoyl peroxide concentrates in the lipid-rich sebaceous follicles. The small amount that is systemically absorbed is converted to benzoic acid, which is further metabolized to benzoate. Benzoate is then excreted in the urine.

The systemic exposure to dapsone 5% gel (Aczone) versus oral dapsone 100 mg was studied for 14 days. The results indicated that twice daily topical application of the agent leads to less systemic exposure to the drug than the 100 mg once daily oral administration of the drug. Patients applying the drug topically had approximately 100-times less exposure to the active drug, as measured by the area-under-the curve (AUC), than patients taking the drug orally.

Tazarotene (Tazorac, Fabior) is converted by ester hydrolysis to its active metabolite, tazarotenic acid. There is little parent compound absorbed in the plasma, and the small amount is highly plasma protein-bound. Tazarotenic acid is eliminated by the urinary and fecal routes. Tazarotene gel and cream have a half-life of about 18 hours. Tazarotene foam has a half-life of about 8 hours.

Tretinoin (Atralin, Avita, Retin A, Retin-A Micro, Tretin-X) has only been found in trace amounts in plasma when applied topically. It is a metabolite of Vitamin A.

Topically administered salicylic acid results in percutaneous absorption, yet systemic exposure is negligible with normal use. Approximately 10% of applied salicylates can remain in the skin after dermal application, while acute toxicity is rarely seen.

Sulfacetamide (Klaron, Ovace, Ovace Plus, Ovace Plus Wash) is approximately 4% bioavailable and is excreted in the urine unchanged. The half-life of sulfacetamide varies between 7 and 13 hours. Absorption through intact skin has not been determined for sodium sulfacetamide (Avar, Avar E, Avar E-LS, Avar LS, BP 10-1, BP Cleansing Wash, Plexion, Rosanil, Rosula, SSS 10-5, SulfaCleanse, Sumadan, Sumadan XLT, Sumaxin, Zencia). Approximately 1% of topical sulfur is systemically absorbed.

Pharmacokinetic studies with adapalene (Differin) and the combination product with benzoyl peroxide (Epiduo, Epiduo Forte) have only found trace amounts of adapalene in plasma when administered topically. Excretion is primarily by the biliary route.

Azelaic acid (Azelex) is approximately 4% bioavailable, and any absorbed drug is excreted unchanged in the urine. Its half-life is about 12 hours.

CONTRAINDICATIONS/WARNINGS^{156,157,158,159,160,161,162,163,164,165,166,167,168,169,170,171,172,173,174,175,176,177,178,179,180,181,182,183,184,185,186,187,188,189,190,191,192,193,194,195}

Products containing clindamycin or erythromycin (Acanya, Benzacilin, Benzamycin, Benzamycin Pak, Duac, Neuac, Onexton, Cleocin T, Clindagel, Clindacin P, Clindacin PAC, Clindacin ETZ, Evoclin, Veltin, Ziana) are contraindicated in patients with a history of regional enteritis, ulcerative colitis, or antibiotic-associated colitis. Sulfacetamide (Avar, Avar E, Avar E-LS, Avar LS, BP Cleansing Wash, Klaron, Ovace, Ovace Plus, Ovace Plus Wash, Plexion, Rosanil, SSS 10-5, SulfaCleanse, Sumadan, Sumaxin, Zencia) is contraindicated in patients with hypersensitivity to sulfonamides. Sodium sulfacetamide/sulfur is not to be used by patients with kidney disease. Tazarotene (Fabior, Tazorac) is contraindicated in pregnant women or women who may become pregnant.

Topical dapsone gel (Aczone) is contraindicated in persons with a hypersensitivity to dapsone and any other component in the formulation. Patients with glucose-6-phosphate dehydrogenase (G6PD) deficiency or congenital or idiopathic methemoglobinemia using dapsone gel are more susceptible to drug induced methemoglobinemia. Avoid use of dapsone gel (Aczone) in patients with congenital or idiopathic methemoglobinemia. Topical administration of dapsone gel did not demonstrate peripheral neuropathy or skin reactions as reported with oral administration. Oral dapsone has produced dose-related hemolysis and hemolytic anemia.

For patients using adapalene- (Differin, Epiduo, Epiduo Forte), tretinoin- (Atralin, Avita, Retin-A, Retin-A Micro, Tretin-X, Veltin, Ziana), or benzoyl peroxide-containing products, excessive or prolonged exposure to sunlight should be limited. Patients taking other photosensitizing medications should use additional caution. Weather extremes, such as wind or cold, may also be irritating. Patients should use caution to avoid contamination of hair, fabrics, and carpet with benzoyl peroxide products as bleaching and/or discoloration may result.

Erythema, scaling, dryness, and stinging/burning may be experienced with the use of adapalene/benzoyl peroxide gel (Epiduo, Epiduo Forte). These reactions are most likely to occur during the first 4 weeks of treatment. Reactions are generally mild to moderate in intensity and typically lessen with continued use. Depending upon severity, patients should be advised to use a moisturizer and/or reduce the frequency of application.

Adapalene/benzoyl peroxide gel should not be applied to cuts, abrasions, eczematous, or sunburned skin. As with other retinoids, the use of 'waxing' as a depilatory method should be avoided on skin surfaces treated with adapalene/benzoyl peroxide gel.

Pseudomembranous colitis has been reported with bacterial agents such as clindamycin and erythromycin, ranging in severity from mild to life-threatening, when administered orally or parenterally. Absorption of these antibiotics through the skin is minimal, however.

Concomitant topical acne treatment, as well as cosmetic products with drying effects, should be used with caution, as possible cumulative irritancy may occur.

During the early weeks of therapy, apparent exacerbations of acne may occur. This is caused by the product's action on previously unseen lesions and should not be viewed as a reason to discontinue therapy.

Fatalities have rarely occurred due to severe reactions to sulfonamides such as sulfacetamide. Sulfacetamide also contains sodium metabisulfite, which may cause allergic-type reactions in patients.

Azelaic acid (Azelex) can cause hypopigmentation. Tretinoin (Atralin, Avita, Retin-A, Retin-A Micro, Tretin-X) may cause temporary hyper- or hypopigmentation.

Contact with eyes, eyelids, lips, and mucous membranes should be avoided. Breaks in the skin should also not come into contact with these products.

Avoid fire, flame, and smoking following use of any gel; they are flammable.

Salicylic acid agents are contraindicated in patients with hypersensitivity to salicylates. In concentrations greater than 6%, salicylic products are contraindicated in patients with diabetes mellitus and other conditions of poor blood circulation such as peripheral vascular disease. Caution should be applied when administering salicylic products in children and adolescents with varicella or influenza due to the potential for Reye's syndrome.

Avoid prolonged usage of salicylic acid over large areas in children and patients with renal impairment or hepatic disease due to the increase the risk of developing salicylism.

Tretinoin (Atralin) gel contains soluble fish proteins and should be used with caution in patients with known sensitivity or allergy to fish.

DRUG INTERACTIONS^{196,197,198,199,200,201,202,203,204,205,206,207,208,209,210,211,212,213,214,215,216,217,218,219,220,221,222,223,224,225,226,227,228,229,230,231}

Concomitant use with cosmetics, medicated or abrasive soaps and cleansers, alcohol, astringents, spices, or lime grind or other agents that have a strong drying effect should be avoided. Benzoyl peroxide potentiates adverse effects seen with tretinoin during concurrent use.

Levels of dapsone and its metabolites, N-acetyl-dapsone (NAD) and dapsone hydroxylamine (DHA), increased when co-administered with trimethoprim-sulfamethoxazole. Temporary local yellow or orange discoloration of the skin and facial hair was seen when topical administration of dapsone was followed by benzoyl peroxide. Concomitant medications such as rifampin, anticonvulsants, and St. John's Wort may increase the formation of DHA, which is associated with hemolysis.

Topical erythromycin-containing products and topical clindamycin-containing products should not be administered concomitantly due to the potential antagonism of effect. Other concomitant topical acne therapies should be used with caution in order to prevent cumulative irritancies.

Dapsone can cause elevated methemoglobin levels when used concomitantly with drugs that induce methemoglobinemia such as sulfonamides, acetaminophen, acetanilide, aniline dyes, benzocaine, chloroquine, dapsone, naphthalene, nitrates and nitrites, nitrofurantoin, nitroglycerin, nitroprusside, pamaquine, para-aminosalicylic acid, phenacetin, phenobarbital, and phenytoin, primaquine.

Clindamycin has been shown to have neuromuscular blocking properties that may enhance the action of other neuromuscular blocking agents. Therefore, caution should be taken when using clindamycin-containing products with neuromuscular blocking agents.

Concomitant use of salicylic acid with other drugs which may contribute to elevated serum salicylate levels (e.g., oral aspirin and other salicylate containing medications, such as sports injury creams) should be avoided.

Sulfonamides (Avar, Avar E, Avar E-LS, Avar LS, BP Cleansing Wash, Klaron, Ovace, Ovace Plus, Ovace Plus Wash, Plexion, Rosanil, SSS 10-5, SulfaCleanse, Sumadan, Sumadan XLT, Sumaxin, Zencia) are incompatible with preparations containing silver and should not be applied to the same sites as products containing silver salts, including preparations such as silver nitrate, silver sulfadiazine, or mild silver protein.

Tazarotene (Fabior, Tazorac) should be administered with caution if the patient is also taking drugs known to be photosensitizers, such as thiazides, tetracyclines, fluoroquinolones, phenothiazines, or sulfonamides, because of the increased possibility of augmented photosensitivity. Formal drug-drug interaction studies were not conducted with Fabior foam.

ADVERSE EFFECTS^{232,233,234,235,236,237,238,239,240,241,242,243,244,245,246,247,248,249,250,251,252,253,254,255,256,257,258,259,260,261,262,263,264,265,266,267,268,269,270,271,272,273}

Drug	Erythema	Peeling	Dryness	Burning/ Stinging	Itching	Photosensitivity
adapalene (Differin)	10-40	10-40	10-40	10-40	10-40	<1
adapalene/ benzoyl peroxide (Epiduo)	1-15	nr	1-13	9-14	nr	nr
adapalene/ benzoyl peroxide (Epiduo Forte)	1-20	nr	2-15	6-19	nr	nr
azelaic acid (Azelex)	<1	<1	<1	1-5	1-5	nr
benzoyl peroxide (AcneFree) (AcneFree Severe) (Acne Medication) (Acne Spot Treatment) (Advanced Acne Wash) (BP) (BP Foam) (BP Foaming Wash) (BP Gel) (BPO) (BP Wash) (Dual Action Cleanser [OTC]) (Effaclar Duo) (OC8) (Pacnex) (Pacnex HP) (Pacnex LP) (Panoxyl) (Panoxy-4) (Persa-Gel) (Riax)	reported	reported	reported	reported	reported	nr
benzoyl peroxide (Benzefoam/Benzefoam Ultra, BenzePro)	nr	nr	reported	nr	nr	nr
benzoyl peroxide (Inova)	reported	nr	reported	reported	nr	nr

Adverse Effects (continued)

Drug	Erythema	Peeling	Dryness	Burning/ Stinging	Itching	Photosensitivity
benzoyl peroxide/ clindamycin (Acanya)	2-25	0.1	nr	1-8	1-15	Nr
benzoyl peroxide/ clindamycin (BenzaClin)	1	2	12	nr	2	1
benzoyl peroxide/ clindamycin (Duac) (Neuac)	5-26	2-17	1-15	<1-5	nr	nr
benzoyl peroxide/clindamycin (Onexton)	<1-28	nr	nr	<1-7	3-15	nr
benzoyl peroxide/ erythromycin (Benzamycin)	reported	reported	3	3	reported	nr
benzoyl peroxide/ erythromycin (Benzamycin Pak)	2.5	0.5	7.6	2.5	1.7	1.3
benzoyl peroxide/hydrocortisone (Vanoxide-HC)	nr	nr	nr	reported	nr	nr
benzoyl peroxide/ salicylic acid (Inova 4/1) (Inova 8/2)	reported	reported	reported	reported	reported	reported
benzoyl peroxide/ sulfur (NuOx)	5	5	nr	nr	nr	nr
clindamycin (Cleocin T)	7-16	7-11	18-23	11	7-11	nr
clindamycin (Clindacin P) (Clindacin PAC) (Clindacin ETZ)	16	11	19	11	7	nr
clindamycin (Clindagel)	nr	0.6	nr	nr	0.6	nr
clindamycin (Evoclin)	nr	nr	1	6	1	nr
dapsone (Aczone)	5-9	6-13	3-14	1	1	nr

Adverse Effects (continued)

Drug	Erythema	Peeling	Dryness	Burning/ Stinging	Itching	Photosensitivity
erythromycin (Erygel) (Ery)	reported	reported	reported	reported	reported	nr
salicylic acid (Acne Control Cleansing) (Acne Cream) (Acne Pads) (Acne Treatment) (Advanced Acne Spot Treatment) (Cleansing Pads) (Clearasil Daily Clear) (Oil-Free Acne Wash) (Rapid Clear)	nr	reported	reported	reported	reported	nr
sodium sulfacetamide (Klaron)	<1	nr	nr	reported	<1	nr
sodium sulfacetamide (Ovace) (Ovace Plus) (Ovace Plus Wash)	nr	nr	nr	reported	nr	nr
sodium sulfacetamide/sulfur (Avar) (Avar E) (Avar E LS) (Avar LS) (BP 10-1) (BP Cleansing Wash) (Plexion) (Rosanil) (Rosula) (SSS 10-5) (SulfaCleanse) (Sumadan) (Sumadan XLT) (Sumaxin) (Zencia)	reported	reported	reported	reported	reported	reported
tazarotene (Fabior)	6	reported	7	reported	1	reported
tazarotene (Tazorac)	10-30	10-30	10-30	10-30	10-30	reported

Adverse Effects (continued)

Drug	Erythema	Peeling	Dryness	Burning/ Stinging	Itching	Photosensitivity
tretinoin (Atralin)	7	12	16	8	2	1
tretinoin (Avita)	reported	reported	reported	reported	reported	reported
tretinoin (Retin-A)	reported	nr	nr	nr	nr	reported
tretinoin (Retin-A Micro)	reported	reported	reported	reported	reported	reported
tretinoin (Tretin-X)	reported	reported	reported	reported	reported	reported
clindamycin/tretinoin (Ziana)	26	17	1	4	4	reported
clindamycin/tretinoin (Velitin)	4	5	6	reported	2	1

Adverse effects data are reported as percentages and obtained from package inserts and are not meant to be comparative or all inclusive. During the first weeks of treatment, cutaneous adverse effects may occur. These effects typically lessen with continued use of the product, and are reversible with discontinuation of use. nr = not reported.

SPECIAL POPULATIONS^{274,275,276,277,278,279,280,281,282,283,284,285,286,287,288,289,290,291,292,293,294,295,296,297,298,299,300,301,302,303,304,305,306,307,308,309,310}

Pediatrics

The safety and effectiveness of all these products in patients younger than 12 years of age have not been established; the exceptions are benzoyl peroxide (Nuox), which has been approved for patients as young as 6 years of age, tretinoin (Atralin), which has been studied in children as young as 10 years of age, and adapalene/benzoyl peroxide (Epiduo) in children as young as 9 years of age.

Pregnancy

Tazarotene (Fabior, Tazorac) is a teratogenic substance; it is not known what level of exposure causes teratogenicity in humans. Tazarotene is classified as Pregnancy Category X. Other retinoids may cause fetal harm in pregnant women; tretinoin (Atralin, Avita, Retin-A, Retin-A Micro, Tretin-X), adapalene (Differin), clindamycin/benzoyl peroxide (Acanya), and clindamycin/tretinoin (Velitin, Ziana) are Pregnancy Category C.

The safety and effectiveness of salicylic acid in pregnancy women is not well studied. Salicylic acid should only be used during pregnancy if the potential benefits to the mother outweigh the potential risk to the fetus.

All other reviewed agents are Pregnancy Category C, with the exception of clindamycin and erythromycin products, which are Pregnancy Category B.

Patients with deficiency of glucose-6-phosphate dehydrogenase (G6PD)

A double-blind, randomized, vehicle-controlled, crossover study with patients aged 12 years and older with G6PD deficiency and acne vulgaris reported a decrease in hemoglobin concentration by 0.32 g/dL from baseline to 2 weeks during treatment with dapsone 5% gel treatment.³¹¹ No other changes in other laboratory parameters were reported up to 12 weeks with continued treatment. No clinical signs or symptoms of hemolytic anemia were noted.

DOSAGES^{312,313,314,315,316,317,318,319,320,321,322,323,324,325,326,327,328,329,330,331,332,333,334,335,336,337,338,339,340,341,342,343,344,345,346,347,348,349,350,351,352,353}

Drug	Instructions	Availability
adapalene (Differin)	apply thin film to affected area(s) once daily at after washing as directed	0.1% cream, lotion (Rx-only) 0.1 % gel (tube) (Rx and OTC) 0.3% gel, gel pump
adapalene/ benzoyl peroxide (Epiduo, Epiduo Forte)	apply thin film to affected areas once daily after washing	Epiduo: 0.1/2.5% gel, gel pump Epiduo Forte: 0.3/2.5% gel pump
azelaic acid (Azelex)	apply to affected areas	20% cream
benzoyl peroxide	apply once or twice daily as directed	10% cream 2.5,5,10% gel* 3 , 4, 5, 6, 7 (Rx-only), 9 , 10 % cleanser* 5.3, 9.8% emollient foam 10% lotion*
benzoyl peroxide (AcneFree)	apply twice daily (morning and evening) to affected area as directed	Kit containing 2.5% benzoyl peroxide cleanser, toner, retinol complex, and 3.7% benzoyl peroxide repair lotion*
benzoyl peroxide (AcneFree Severe)	use cleanser twice daily in the morning and evening; use repair lotion once daily in the morning use other kit ingredients (e.g., toner, retinol complex) as directed	Kit containing 2.5% benzoyl peroxide cleanser, toner, retinol complex, and 10% benzoyl peroxide repair lotion*
benzoyl peroxide (Acne Medication)	apply 1 to 3 times daily as directed	5, 10% gel* 5, 10% lotion*
benzoyl peroxide (Acne Spot Treatment)	apply 1 to 3 times daily as directed	2, 2.5% cream*
benzoyl peroxide (Advanced Acne Wash)	apply once or twice daily as directed	4.4% cleanser ER*
benzoyl peroxide (Benzefoam)	apply once daily as directed	5.3% foam

Dosages (continued)

Drug	Instructions	Availability
benzoyl peroxide (BenzeFoam Ultra)	apply once daily as directed	9.8% foam
benzoyl peroxide (BenzePro)	apply once to 3 times daily as directed	7% cleanser 5.3, 9.8% foam 6% towelette
benzoyl peroxide (BP)	apply 1 to 3 times as directed	5, 10% gel*
benzoyl peroxide (BP Foam)	apply 1 to 3 times as directed	5.3% foam 9.8% foam
benzoyl peroxide (BP Foaming Wash)	apply 1 to 3 times as directed	10% cleanser
benzoyl peroxide (BP Gel)	apply 1 to 3 times as directed	5.5% gel*
benzoyl peroxide (BP Wash)	apply 1 to 3 times as directed	2.5*, 5, 7*, 10% cleanser 4/5%, 8/5% cleanser kit
benzoyl peroxide (BPO)	apply once to twice daily as directed	4, 8% gel 4/5%, 8/5% cleanser kit* 6, 9% towelette
benzoyl peroxide (BPO-5)	apply once to twice daily as directed	5% cleanser*
benzoyl peroxide (BPO-10)	apply once to twice daily as directed	10% cleanser*
benzoyl peroxide (Dual Action Cleanser)	apply as directed	3.5% cleanser*
benzoyl peroxide (Effaclar Duo)	apply as directed	5.5% solution*
benzoyl peroxide (Inova)	apply 1 to 3 times as directed	4/5% combo package with vitamin E oil 8/5% combo package with vitamin E oil
benzoyl peroxide (OC8)	apply once or twice daily as directed	7% gel*
benzoyl peroxide (Pacnex)	apply once or twice daily as directed	7% cleanser
benzoyl peroxide (Pacnex HP)	apply once or twice daily as directed	7% med pad
benzoyl peroxide (Pacnex LP)	apply once or twice daily as directed	4.25% med pad
benzoyl peroxide (Panoxyl)	apply once or twice daily as directed	3% cream* 10% bar, cleanser*
benzoyl peroxide (Panoxyl-4)	apply once or twice daily as directed	4% cleanser*

Dosages (continued)

Drug	Instructions	Availability
benzoyl peroxide (Persa-Gel)	apply once or twice daily as directed	10% gel*
benzoyl peroxide (Riax)	apply 1 to 3 times as directed	5.5, 9.5% foam
benzoyl peroxide/clindamycin (Acanya)	apply a pea size amount once daily to the face	2.5/1.2% gel pump
benzoyl peroxide/clindamycin (BenzaClin)	apply twice daily or as directed	5/1% gel, gel pump
benzoyl peroxide/clindamycin (Duac)	apply once daily after washing as directed	5/1.2% gel
benzoyl peroxide/clindamycin (Neuac)	apply once daily, in the evening, after washing as directed	5/1.2%gel 5/1.2% gel Kit with Niseko (sunscreen SPF 25)
benzoyl peroxide/clindamycin (Onexton)	apply pea sized amount to the face once daily	1.2/3.75% gel, gel pump
benzoyl peroxide/erythromycin (Benzamycin) (Benzamycin Pak)	apply twice daily as directed	5/3% gel
benzoyl peroxide/hydrocortisone (Vanoxide-HC)	apply as directed	5/0.5% suspension benzoyl peroxide bulk powder and hydrocortisone
benzoyl peroxide/salicylic acid (Inova 4/1)	apply once or twice daily (morning and evening) after washing as directed	4/1% combo package benzoyl peroxide/salicylic acid pads
benzoyl peroxide/salicylic acid (Inova 8/2)	apply once or twice daily (morning and evening) after washing as directed	8/2% combo package benzoyl peroxide/salicylic acid pads
benzoyl peroxide/sulfur (NuOx)	ages 6 to 12: apply once daily as tolerated ages 12 and older: apply daily during the first week, then twice daily thereafter as tolerated	6/3% gel
clindamycin	apply twice daily to affected areas	1% foam, gel, lotion, solution, med swab
clindamycin (Cleocin T)	apply twice daily to affected areas	1% gel, lotion, med swab, solution
clindamycin (Clindacin P)	apply twice daily to affected areas	1% med swabs
clindamycin (Clindacin PAC) (Clindacin ETZ)	apply twice daily to affected areas	1% med swab, kit with cleanser (Acuwash-skin cleanser combo 19)
clindamycin (Clindagel)	apply once daily to affected areas	1% gel
clindamycin (Evoclin)	apply once daily to affected areas	1% foam

Dosages (continued)

Drug	Instructions	Availability
dapsone (Aczone)	5%- apply pea-sized amount twice a day to affected areas 7.5%- apply pea-sized amount to face once daily; can also apply thin layer to other affected areas once daily	5% gel (tube) 7.5% gel (pump)
erythromycin	apply twice daily to affected areas	2% gel, med pad, solution
erythromycin (Ery)	apply to affected area twice daily (morning and evening as directed	2% med pad
erythromycin (Erygel)	apply once or twice daily to affected area(s) as directed	2% gel
salicylic acid (Clearasil Daily Clear)	Apply as directed to affected areas	1%, 2% med pad* 2% cleanser* 10% cream*
salicylic acid (Oil free Acne Wash)	Apply as directed to affected areas	2% cleanser*
salicylic acid (Advanced Acne Spot Treatment)	Cover the entire affected area with a thin layer 1 to 3 times a day.	2% lotion*
salicylic acid (Acne Pads) (Cleansing Pads) (Rapid Clear)	Apply as directed to affected areas	2% med pad*
salicylic acid (Acne Cream) (Acne Control Cleanser) (Acne Treatment)	Apply as directed to affected areas	10% cream*
sodium sulfacetamide	apply as directed	10% cleanser, cleanser gel, shampoo, suspension
sodium sulfacetamide (Klaron)	apply twice daily to affected areas	10% topical suspension
sodium sulfacetamide (Ovace)	apply once or twice daily as directed	10% cleanser
sodium sulfacetamide (Ovace Plus)	foam: apply 1 to 3 times daily to affected areas as directed cleanser ER, cream, lotion, shampoo: apply twice daily (morning and evening) to affected area as directed	9.8% foam, lotion 10% cream 10% shampoo 10% cleanser ER
sodium sulfacetamide (Ovace Plus Wash)	apply once or twice daily as directed	10% cleanser gel ER

Dosages (continued)

Drug	Instructions	Availability
sodium sulfacetamide/sulfur	apply 1 to 3 times daily to affected areas as directed	8/4% suspension 9/4% cleanser 9/4.5% cleanser, kit 9.8/4.8% cleanser, cream, lotion 10% lotion 10/2% cream, cleanser 10/4% med pads 10/5% gel, lotion, cleanser, cream, foam, lotion, , suspension
sodium sulfacetamide/sulfur (Avar)	apply 1 to 3 times daily to affected areas as directed	9.5/5% foam, med pad 10/5% cleanser
sodium sulfacetamide/sulfur (Avar E) (Avar E-Green)	apply 1 to 3 times daily to affected areas as directed	10/5% cream
sodium sulfacetamide/sulfur (Avar E-LS)	apply 1 to 3 times daily to affected areas as directed	10/2% cream
sodium sulfacetamide/sulfur (Avar LS)	apply 1 to 3 times daily to affected areas as directed	10%/2% cleanser, foam, med pad
sodium sulfacetamide/sulfur (BP 10-1)	apply 1 to 3 times daily to affected areas as directed	10%/1% cleanser
sodium sulfacetamide/sulfur (Plexion)	apply to affected area as directed	9.8%/4.8% cream, cleanser, med pad, lotion
sodium sulfacetamide/sulfur (Rosanil)	apply once or twice daily as directed	10%/5% cleanser
sodium sulfacetamide/sulfur (Rosula)	apply once or twice daily as directed	10/4.5% cleanser 10/5% med pad
sodium sulfacetamide/sulfur (SSS 10-5)	apply 1 to 3 times daily to affected areas as directed	10/5% cream 10/5% foam
sodium sulfacetamide/sulfur (Sumadan)	apply once or twice daily as directed	9/4.5% cleanser 9/4.5% kit In a vehicle containing green tea & aloe
sodium sulfacetamide/sulfur (Sumadan XLT)	apply once or twice daily as directed	9/4.5% kit with Niseko (sunscreen Broad spectrum SPF 25)
sodium sulfacetamide/sulfur (Sumaxin)	apply once or twice daily as directed	10/4% med pads 9/4% cleanser
sodium sulfacetamide/sulfur (Sumaxin CP)	apply once or twice daily as directed	10/4% kit with Rehlya Daily Wash
sodium sulfacetamide/sulfur (SulfaCleanse) (Sumaxin TS)	apply once or twice daily as directed	8/4% suspension In a vehicle containing green tea & aloe

Dosages (continued)

Drug	Instructions	Availability
sodium sulfacetamide/sulfur (Zencia)	apply once or twice daily as directed	9/4% cleanser
sodium sulfacetamide/sulfur/urea vehicle (BP Cleansing Wash)	apply once or twice daily as directed	10/4/10%, 10/5/10% cleanser
tazarotene (Fabior)	apply a thin layer once daily in the evening	0.1% foam
tazarotene (Tazorac)	apply a thin film once daily in the evening to affected areas after washing	0.05, 0.1% cream, gel
tretinoin	apply once daily in the evening to affected area after washing	0.025, 0.05, 0.1% cream 0.025, 0.01, 0.05% gel
tretinoin microspheres	apply a thin layer once daily, before bedtime, to affected areas after washing	0.04, 0.1% gel, gel pump
tretinoin (Atralin)	apply once daily at bedtime to affected areas after washing	0.05 % gel
tretinoin (Avita)	apply once daily in the evening to affected area after washing	0.025 % cream 0.025 % gel
tretinoin (Retin-A)	apply once daily in the evening to affected area after washing	0.025, 0.05, 0.1% cream 0.025, 0.01% gel
tretinoin (Retin-A Micro)	apply a thin layer once daily, before bedtime, to affected areas after washing	0.04, 0.1% gel, gel pump 0.08% gel pump
tretinoin (Tretin-X)	apply a thin layer once daily, before bedtime, to affected areas	0.025, 0.05, 0.1%, combo package 0.0375, 0.075% cream
clindamycin/tretinoin (Ziana)	apply once daily at bedtime to face after washing	1.2/0.025% gel
clindamycin/tretinoin (Veltin)	apply once daily in the evening to affected areas	1.2/0.025% gel

* Products available without prescription (over-the-counter). Other products are available by prescription only.

Before application of these products, the affected skin should be thoroughly washed, rinsed with warm water, and patted dry. Benzamycin requires the addition of ethyl alcohol and must be refrigerated following reconstitution.

CLINICAL TRIALS

Search Strategy

Articles were identified through searches performed on PubMed and review of information sent by manufacturers. Search strategy included the use of all drugs in this class and acne vulgaris. Randomized controlled comparative trials for FDA-approved indications are considered the most relevant in this category. Studies included for analysis in the review were published in English, performed with human participants, and randomly allocated participants to comparison groups. In addition, studies must contain clearly stated, predetermined outcome measure(s) of known or probable clinical importance, use data analysis techniques consistent with the study question, and include follow-up (endpoint assessment) of at least 80% of participants entering the investigation. Despite some inherent bias found in all studies including those sponsored and/or funded by pharmaceutical manufacturers, the studies in this therapeutic class review were determined to have results or conclusions that do not suggest systematic error in their experimental study design. While the potential influence of manufacturer sponsorship and/or funding must be considered, the studies in this review have also been evaluated for validity and importance.

There were many studies found using these criteria. Only comparative studies were included, and studies of the active drug compared to placebo or vehicle were not included. Unacceptable data were determined to be those studies with any of the following characteristics: low number of patients enrolled, comparator drug not available in the U.S., manufacturer-sponsored, open-label, pooled data, unavailable strengths in U.S., use of different formulations of the same active ingredient, inadequate treatment duration, or split-face treatment. Many studies use the investigator-blinded design rather than using the double-blinded method.

adapalene (Differin) versus benzoyl peroxide/clindamycin (Duac)

A randomized, assessor-blind study enrolled 130 patients with mild to moderate facial acne vulgaris to compare benzoyl peroxide 5%/clindamycin 1% gel and adapalene 0.1% gel for 12 weeks.³⁵⁴ Lesion counts, acne grade, and global improvement were assessed at weeks 1, 2, 4, 8, and 12. Both agents were effective, but benzoyl peroxide 5%/clindamycin 1% gel had a faster onset of action and a faster significant reduction in inflammatory and total lesion counts compared with adapalene gel. There was a statistically significant difference for both inflammatory lesions ($p \leq 0.001$) and total lesions ($p \leq 0.004$), between benzoyl peroxide 5%/clindamycin 1% gel versus adapalene gel, starting at week 1 and continuing onward. Inflammatory lesions remaining at week 2 in benzoyl peroxide 5%/clindamycin 1% gel versus adapalene gel were 55% versus 76%, respectively. At week 2, benzoyl peroxide 5%/clindamycin 1% gel removed 38% more inflammatory lesions than adapalene gel. The trend in favor of benzoyl peroxide 5%/clindamycin 1% gel continued but was less marked for the remainder of the study. Benzoyl peroxide 5%/clindamycin 1% gel was better tolerated than adapalene gel.

adapalene (Differin) versus benzoyl peroxide/clindamycin (Duac) versus benzoyl peroxide/clindamycin plus adapalene

A multicenter, parallel-group, single-blind study of 109 patients measured the efficacy and safety of benzoyl peroxide 5%/clindamycin 1% gel, adapalene 0.1% gel, and the combination.³⁵⁵ Primary endpoints were inflammatory, noninflammatory, and total lesion counts at weeks 2, 4, 8, and 12. Lesion count reduction and percentage change at week 12 were highest in the combination therapy

group ($p=NS$) and lowest in the adapalene group ($p=NS$). Taken individually, the combination group had higher reductions in noninflammatory lesions and total lesions compared to the adapalene group (both $p<0.05$). At week 12, there were no significant differences among groups with regard to erythema, dryness, or peeling. A separate analysis of the adverse events showed that the patients in the combination therapy group had less erythema than patients in the adapalene group ($p<0.05$).

adapalene (Differin) versus tazarotene (Tazorac)

A multicenter, double-blind, randomized, parallel-group study enrolled 164 patients with mild to moderate facial acne vulgaris to receive 15 weeks of treatment with alternate-day tazarotene 0.1% gel and vehicle gel on the intervening evenings or once daily adapalene 0.1% gel.³⁵⁶ Both regimens were comparably effective with no significant between-group differences in efficacy measures. A total of 74% of tazarotene-treated subjects and 73% of adapalene-treated subjects achieved at least a 50% improvement in their acne. In addition, there were no clinically significant differences in tolerability. It appears that tazarotene treatment can be useful even in patients whose compliance may be suboptimal.

The efficacy and tolerability of tazarotene 0.1% gel and adapalene 0.1% gel were compared in a multicenter, double-blind, randomized, parallel-group study in 145 patients with mild to moderate facial acne vulgaris.³⁵⁷ Both treatments were applied once daily in the evenings for up to 12 weeks. Treatment with tazarotene was associated with a significantly greater incidence of treatment success ($\geq 50\%$ global improvement with 78% versus 52%; $p=0.002$), significantly greater reductions in overall disease severity ($p<0.0001$), non-inflammatory lesion count ($p<0.0001$), and inflammatory lesion count ($p=0.0002$) compared with adapalene. In the early weeks of treatment, tazarotene was associated with greater levels of burning, pruritus, erythema, and peeling compared with adapalene ($p<0.01$); however, at the end of treatment, patients considered both treatments to be comparably well tolerated.

adapalene (Differin) versus tretinoin

A dose range effect of 2 concentrations of adapalene gel as acne treatment was evaluated, as well as a comparison of adapalene 0.1% gel with tretinoin 0.025% gel in the treatment of acne patients using two multicenter, investigator-masked, parallel group studies.³⁵⁸ In the dose range study, 89 patients were enrolled, and 591 patients were in the concurrent controlled studies. Adapalene 0.1% gel was significantly more effective in treating acne lesions than adapalene gel 0.03%. Adapalene gel 0.1% was significantly more effective than tretinoin 0.025% gel in 1 study and of the same effectiveness in the other study. Adapalene gel was better tolerated than tretinoin gel.

The 10-week, multicenter, randomized, investigator-masked, active-controlled, parallel-group study compared adapalene 0.1% gel with tretinoin 0.05% cream in 409 patients with mild to moderate acne vulgaris.³⁵⁹ Adapalene 0.1% gel demonstrated equivalent efficacy in reduction of acne lesion counts and global improvement of acne severity over 10 weeks. Adapalene 0.1% gel was significantly better tolerated than tretinoin cream 0.05% in terms of erythema, dryness, desquamation, and stinging/burning.

To determine the tolerability and efficacy of adapalene 0.1% gel versus tretinoin 0.1% microsphere gel in 168 patients with acne vulgaris, a 12-week, multicenter, randomized, controlled, investigator-masked, parallel-group study was conducted.³⁶⁰ The efficacy of adapalene 0.1% gel was comparable to that of tretinoin 0.1% microsphere gel, and both treatments had similar onset of action. Cutaneous tolerability

was noted in both groups, with scores significantly better with adapalene 0.1% gel than with tretinoin 0.1% microsphere gel. There were significantly fewer treatment-related adverse events reported with adapalene 0.1% gel.

A randomized, multicenter, investigator-masked study was conducted in 105 patients with mild to moderate acne vulgaris to compare the efficacy and safety of adapalene 0.1% gel with tretinoin 0.025% gel after 3 months of treatment.³⁶¹ In terms of efficacy, adapalene gel was found to be superior to tretinoin gel after 1 week of treatment, with respect to reduction in inflammatory lesion counts (32% versus 17%, respectively; $p=0.001$), total lesion counts (28% versus 22%; $p=0.042$), and global severity grade (28% versus 16%; $p=0.001$). No significant differences between the 2 treatments were found after 12 weeks of treatment for any of these variables. Evaluation of facial skin tolerance parameters showed significant differences between the 2 treatments in favor of adapalene for dryness, erythema, immediate and persistent burning, and pruritus for at least 1 time point. Quality of life scores improved more rapidly in the adapalene group than in the tretinoin group.

A study was designed to compare the efficacy and safety of adapalene 0.1% gel once daily and tretinoin 0.025% gel once daily in the treatment of facial acne vulgaris.³⁶² A total of 323 patients were enrolled for 12 weeks in an investigator-masked, randomized, parallel-group, multicenter trial. Starting at weeks 2 and 4, adapalene produced greater lesion reductions than did tretinoin for all lesion types. By week 12, the mean percent reduction in the different lesion counts was 49% versus 37% for total lesions ($p<0.01$); 46% versus 33% for non-inflammatory lesions ($p=0.02$); and 48% versus 38% for inflammatory lesions ($p=0.06$) in adapalene (Differin) and tretinoin treatment groups, respectively. Adverse effects were limited to a mild dermatitis occurring in both treatment groups.

adapalene 1%/benzoyl peroxide 2.5% (Epiduo) versus adapalene (Differin) versus benzoyl peroxide

A multicenter, double-blind, randomized study involving randomized 517 subjects to adapalene 1%/benzoyl peroxide 2.5% (BPO) gel, adapalene 0.1% in vehicle gel, BPO 2.5% in vehicle gel, or vehicle gel alone. The median age of these subjects was 15 years and 60% were males.³⁶³ At baseline, subjects had between 20 to 50 inflammatory lesions and 30 to 100 non-inflammatory lesions. The majority of subjects had a baseline Investigator's Global Assessment (IGA) of 'moderate', which corresponded to more than half of the face being involved and including many comedones, papules, and pustules. The efficacy results at week 12 showed a two-grade IGA improvement and 'clear' or 'almost clear' rating for 21.5% of the adapalene/BPO group, 12.2% of the adapalene group, 12.1% of the BPO group, and 5.6% of the vehicle group.

A 12-week, randomized, double-blind, parallel-group, active- and vehicle-controlled, multicenter trial compared adapalene 0.1%/benzoyl peroxide 2.5% (BPO) gel, adapalene 0.1% in vehicle gel, BPO 2.5% in vehicle gel, or vehicle gel alone in 1,668 patients with moderate facial acne.³⁶⁴ At 12 weeks, the combination adapalene-BPO gel showed a significantly higher success rate (the percentage of participants with IGA of acne severity rated clear or almost clear; $p\leq 0.006$) and a greater percentage reduction in all acne lesion counts ($p\leq 0.017$) compared with the other treatment groups. A significant early treatment effect of adapalene-BPO combination gel at week 1 compared with adapalene monotherapy and vehicle also was observed for all lesion count reductions ($p<0.001$). Adverse events were similar in all groups.

adapalene 3%/benzoyl peroxide 2.5% (Epiduo Forte) and adapalene 1%/benzoyl peroxide 2.5% (Epiduo)

A double-blind study compared adapalene 3%/benzoyl peroxide 2.5% gel (n=217) to vehicle gel (n=69) in patients with acne vulgaris.³⁶⁵ The study also randomized patients to adapalene 1%/benzoyl peroxide 2.5% gel (n=217). At baseline, 50% of subjects were graded as “moderate” (Grade 3) and 50% were graded as “severe” (Grade 4) on the Investigator’s Global Assessment (IGA) scale. At Week-12, 33.7%, 27.3%, and 11% of patients on 3%/2.5% gel, 1%/2.5% gel, and vehicle gel, respectively experienced at least a 2-grade improvement based on the IGA. There was also a significant improvement in reduction of both inflammatory and non-inflammatory lesion counts with both adapalene/benzoyl peroxide formulations as compared to vehicle. This study was not designed or powered to compare the efficacy of adapalene benzoyl peroxide gel 3%/2.5% gel to the 1%/2.5% gel.

clindamycin versus adapalene (Differin)/clindamycin

A total of 300 patients with acne entered a multicenter, randomized, investigator-blinded study comparing the efficacy and safety of adapalene 0.1% gel combined with clindamycin topical solution 1% versus clindamycin topical solution 1% alone.³⁶⁶ A statistically significant greater reduction was observed from week 4 until week 12 in total lesion counts and from week 8 on for inflammatory and non-inflammatory lesion counts during the initial treatment for combination therapy compared with monotherapy. In the second part of the study (weeks 12 to 24) which was completed by 241 subjects, the efficacy and safety of adapalene alone as maintenance therapy were investigated. Results at week 24 for the reduction in all lesion counts during the maintenance phase were statistically significant in favor of adapalene (41.6%) compared with an increase for all lesion counts in the control group (92.1%). Adapalene alone or in combination with clindamycin topical solution was well tolerated.

A multicenter, randomized, investigator-blinded study evaluated the efficacy and tolerability of adapalene 0.1% gel plus clindamycin 1% lotion compared with clindamycin 1% lotion plus vehicle for the treatment of mild to moderate acne vulgaris in 249 patients.³⁶⁷ Clindamycin was applied twice daily and adapalene or vehicle gel once daily for 12 weeks. Significantly greater reductions of total ($p<0.001$), inflammatory ($p=0.004$), and noninflammatory lesions ($p<0.001$), were seen in the clindamycin/adapalene group than in the clindamycin/vehicle group. These significant treatment effects were observed as early as week 4 for both non-inflammatory and total lesion counts. The worst scores for scaling ($p<0.05$), dryness ($p<0.01$), and stinging/burning ($p<0.05$) were higher in the clindamycin/adapalene group than in the clindamycin/vehicle group.

benzoyl peroxide/clindamycin (Neuac) versus benzoyl peroxide versus clindamycin

Five randomized, double-blind clinical studies evaluated the efficacy of benzoyl peroxide 5%/clindamycin 1.2% combination as compared to benzoyl peroxide, clindamycin, and vehicle.³⁶⁸ There were a total of 1,319 patients within the 5 studies. Patients were instructed to wash the face, wait 10 to 20 minutes, and then apply medication to the entire face, once daily, in the evening before going to bed. Patients were evaluated and their acne lesions were counted at each clinical visit: weeks 2, 5, 8, and 11. The primary efficacy measures were the lesion counts and the investigator’s global assessment evaluated at week 11. Benzoyl peroxide and clindamycin 5%/1.2% gel applied once daily for 11 weeks, was significantly more effective than vehicle, benzoyl peroxide, and clindamycin in the treatment of inflammatory lesions of moderate to moderately severe facial acne vulgaris in 3 of the 5 studies (Studies 1, 2, and 5).

benzoyl peroxide/clindamycin plus adapalene (Differin) versus benzoyl peroxide plus tretinoin microsphere (Retin-A Micro)

A multicenter, randomized, single-blind study of 353 patients measured the efficacy and safety of benzoyl peroxide 5%/clindamycin 1% gel in combination with either adapalene 0.1% gel or tretinoin microsphere 0.04% or 0.1% gel.³⁶⁹ The primary endpoint was investigator global assessment, including variables of lesions counts, global disease severity, and disease signs and symptoms. A trend toward greater reduction in lesions at all time points was seen in the tretinoin 0.04% combination patients, but the difference did not reach statistical significance. The same trend was seen in global disease severity and disease signs and symptoms; none of the differences were statistically significant. Adverse events were minimal and mild in each group.

benzoyl peroxide/clindamycin (Acanya) versus benzoyl peroxide versus clindamycin

The clinical safety and efficacy of benzoyl peroxide (BPO)/clindamycin gel were established in 2 identical, double-blind, randomized, controlled, 12-week, 4-arm studies in which vehicle gels were used as the comparators.^{370,371} A total of 2,813 patients with moderate to severe acne vulgaris aged 12 years or older were randomized to receive BPO/clindamycin, BPO, clindamycin, or vehicle. Safety and efficacy (inflammatory and noninflammatory lesion counts) were evaluated using Evaluator Global Severity Score and subject self-assessment. BPO/clindamycin demonstrated superiority to each individual ingredient and vehicle in reducing both inflammatory and non-inflammatory lesions and acne severity. Visibly greater improvement was observed by patients with BPO/clindamycin as early as week 2. No substantive differences were seen in tolerability among treatment groups; less than 1% of patients discontinued treatment because of adverse events.

benzoyl peroxide/clindamycin (BenzaClin, Duac) versus benzoyl peroxide versus benzoyl peroxide/erythromycin (Benzamycin Pak)

In the randomized, 10-week, multicenter, single-blind trial, 492 patients with moderate to moderately severe acne were treated twice daily with benzoyl peroxide 5%/clindamycin 1%, benzoyl peroxide 5%, or benzoyl peroxide 5%/erythromycin 3% and assessed every 2 weeks.³⁷² Compared with benzoyl peroxide, benzoyl peroxide/clindamycin demonstrated significantly greater reductions in inflammatory lesions ($p=0.04$) and significantly greater overall improvement as assessed by physicians ($p\leq 0.04$) and patients ($p<0.001$). Benzoyl peroxide/clindamycin was not significantly more efficacious than benzoyl peroxide/erythromycin. Dry skin was the most frequent adverse event with all 3 therapies.

clindamycin/benzoyl peroxide (BenzaClin, Duac) versus benzoyl peroxide versus clindamycin

In a 10-week, multicenter, double-blind trial, 480 patients with moderate to moderately severe acne were randomized to receive twice daily treatment with benzoyl peroxide 5% plus clindamycin 1%, benzoyl peroxide 5%, clindamycin 1%, or vehicle.³⁷³ Significantly greater reductions in the number of inflammatory and total lesions were demonstrated in patients using combination therapy compared with those using any of the individual components. Both physicians' and patients' global evaluations showed significantly greater improvements with the combination therapy than with individual components. Dry skin was the most frequent adverse event, occurring to a similar extent in the combination and benzoyl peroxide treatment groups.

A topical gel combining benzoyl peroxide 5% and clindamycin 1% was evaluated in a 10-week, randomized, double-blind trial involving 287 patients with moderate to moderately severe acne.³⁷⁴ The combination demonstrated significantly greater reductions in inflammatory lesions than either of its components alone or vehicle. Significantly greater reductions in comedones and improvements in both physicians' and patients' global evaluations were obtained with the combination compared to clindamycin or vehicle. The reduction in comedones and the global improvements were similar between the combination and benzoyl peroxide. The incidence of dry skin in the combination group was similar to that found with benzoyl peroxide.

dapsone (Aczone) plus adapalene gel (Differin) versus dapsone plus benzoyl peroxide versus dapsone plus moisturizer

A 12-week, randomized, double-blind study of 301 patients with acne evaluated the safety and efficacy of dapsone 5% gel when used in combination with adapalene gel 0.1%, benzoyl peroxide gel 4%, or moisturizer.³⁷⁵ Dapsone gel combined with any of the 3 additional treatments reduced the mean number of inflammatory lesions. However, the reduction of inflammatory lesions was not significant when dapsone was used in combination with adapalene gel or with benzoyl peroxide gel compared to the dapsone plus moisturizer combination group ($p=0.052$ for both versus moisturizer combination). Patients treated with dapsone gel combined with adapalene gel had a significantly better response in reduction in non-inflammatory and total acne lesion count compared to patients who received the moisturizer combination. All treatments were well tolerated.

erythromycin versus clindamycin

A 12-week, investigator-masked, randomized, parallel-group comparison of a gel formulation of erythromycin 2% with clindamycin 1% solution was performed in 102 patients with mild to moderate facial acne vulgaris.³⁷⁶ Both agents were administered twice daily. Both medications significantly reduced the numbers of papules and open and closed comedones. No significant differences in lesion count reductions were detected between the treatment groups after 8 and 12 weeks of treatment.

tazarotene (Tazorac) plus benzoyl peroxide versus tazarotene plus erythromycin/benzoyl peroxide (Benzamycin Pak) versus tazarotene plus clindamycin

A multicenter, investigator-masked, randomized, parallel-group study was performed in 440 patients with mild to moderate facial acne vulgaris to compare the efficacy and tolerability of tazarotene monotherapy with 3 combination regimens.³⁷⁷ Patients received tazarotene plus benzoyl peroxide gel, tazarotene plus erythromycin/benzoyl peroxide gel, or tazarotene plus clindamycin phosphate lotion. The only combination therapy to achieve a significantly greater global improvement than tazarotene monotherapy was tazarotene plus clindamycin. For reducing noninflammatory lesions specifically, none of the combination regimens offered significant benefit over tazarotene monotherapy. For reducing inflammatory lesions, tazarotene plus erythromycin/benzoyl peroxide was significantly more efficacious than all the other regimens. Tazarotene plus clindamycin and tazarotene plus benzoyl peroxide reduced the incidence of adverse effects compared with tazarotene monotherapy; however, the difference was not statistically significant.

tazarotene (Tazorac) plus clindamycin versus tretinoin plus clindamycin

A randomized, investigator-blinded, parallel group, multicenter study compared tazarotene 0.1% cream plus clindamycin 1% gel to tretinoin 0.025% gel plus clindamycin 1% gel in 150 patients with facial acne vulgaris.³⁷⁸ At 12 weeks, the reduction in lesion counts was greater for tazarotene/clindamycin versus tretinoin/clindamycin for both the non-inflammatory lesion count (71% versus 52%, $p \leq 0.01$) and the inflammatory lesion count (77% versus 67%, $p = 0.053$). More patients achieved $\geq 50\%$ global improvement and $\geq 75\%$ global improvement with tazarotene/clindamycin than with tretinoin/clindamycin (88% versus 75%, $p \leq 0.05$ and 66% versus 52% $p = 0.10$, respectively) at week 12. Both regimens were generally well tolerated. This study was supported through a grant from Allergan.

clindamycin/tretinoin (Veltin) versus clindamycin versus tretinoin

The efficacy and safety of clindamycin 1.2% gel and tretinoin 0.025% solubilized in an aqueous-based gel were evaluated in a randomized, double-blind, vehicle-controlled study in 1,649 patients with facial acne vulgaris for 12 weeks.³⁷⁹ The reduction in absolute number of total lesions was greater for clindamycin/tretinoin gel versus clindamycin 1.2% gel and tretinoin 0.025% gel. The reduction in total lesions (55% versus 49%, $p \leq 0.004$) and non-inflammatory lesions (51% versus 43%, $p \leq 0.001$) was greater for clindamycin/tretinoin versus clindamycin, as well as the reduction in total lesions (55% versus 51%, $p < 0.05$) and inflammatory lesions (61% versus 55%, $p \leq 0.004$) versus tretinoin. At 12 weeks, more patients achieved $\geq 40\%$ global improvement with clindamycin/tretinoin than with clindamycin or tretinoin (36% versus 27% and 26%, $p \leq 0.001$ respectively). All 3 regimens were generally well tolerated, although treatment-related application site reactions occurred more frequently with tretinoin and clindamycin/tretinoin (7% and 5%, respectively). This study was supported through a grant from Stiefel.

tazarotene (Tazorac) versus tretinoin

The efficacy and tolerability of tazarotene 0.1% gel and tretinoin 0.1% microsphere gel were evaluated in a multicenter, double-blind, randomized, parallel-group study in 169 patients with mild to moderate inflammatory facial acne vulgaris for 12 weeks.³⁸⁰ Both agents were associated with significant reductions from baseline in the non-inflammatory and inflammatory lesion counts. Tazarotene treatment was associated with a significantly greater incidence of treatment success (defined as $\geq 50\%$ global improvement [67% versus 49%; $p = 0.03$]) and significantly greater reductions in overall disease severity (36% versus 26%; $p = 0.02$) and non-inflammatory lesion count (60% versus 38% at week 12; $p = 0.02$) than tretinoin microsphere treatment. Both drugs were well tolerated.

A multicenter, double-blind, randomized, parallel-group study that compared the efficacy and tolerability of tazarotene and tretinoin was performed in 143 patients with mild to moderate facial acne vulgaris.³⁸¹ Patients were randomized to receive tazarotene 0.1% gel or tretinoin 0.025% gel once daily for 12 weeks. Tazarotene 0.1% gel was more effective than tretinoin 0.025% gel in reducing the open comedone count ($p \leq 0.05$) and the total non-inflammatory lesion count ($p \leq 0.05$). The total inflammatory lesion count was similar ($p = \text{NS}$). At some time points, tazarotene was associated with increased irritation, but peeling, erythema, dryness, burning, and itching never exceeded trace levels.

A 12-week, investigator-blinded, randomized, parallel-design trial compared the safety and efficacy of tretinoin microsphere gel 0.04% to tazarotene cream 0.05% in mild to moderate facial acne vulgaris.³⁸²

Efficacy measurements included IGA, lesion counts, and subject self-assessment of acne signs and symptoms. Efficacy was generally comparable between treatment groups, although tretinoin provided more rapid results in several parameters. IGA showed a more rapid mean change from baseline at week 4 in the tretinoin group (-0.18 versus -0.05 in the tazarotene group). Tretinoin improved papules more rapidly. At week 4, the mean percentage change from baseline in open comedones was statistically significant at -64% in the tretinoin group ($p=0.0039$, within group) versus -19% in the tazarotene group (not statistically significant within the group; $p=0.1875$). Beginning with week 4, skin dryness, peeling, and pruritus were significantly lower in the tretinoin group. Both groups had a low incidence of adverse events.

META-ANALYSES

A meta-analysis evaluating efficacy of benzoyl peroxide (BPO), clindamycin, BPO/salicylic acid, and combination of BPO/clindamycin using the Cochrane collaboration guidelines included a total of 23 studies including 7,309 patients with acne.³⁸³ At 2 to 4 weeks, BPO/salicylic acid had a statistically greater percentage of lesion reductions over other groups (weighted mean inflammatory lesion reduction: BPO 33.4%, clindamycin 21.5%, BPO/salicylic acid 55.2%, BPO/clindamycin 40.7%, placebo 7.3%; weighted mean non-inflammatory lesion reduction: BPO 19.1%, clindamycin 10%, BPO/salicylic acid 42.7%, BPO/clindamycin 26.2%, placebo 6.7%). At 10- to 12-week endpoints, BPO/salicylic acid and BPO/clindamycin were similar (weighted mean inflammatory lesion reduction: BPO 43.7%, clindamycin 45.9%, BPO/salicylic acid 51.8%, BPO/clindamycin 55.6%, placebo 26.8%; weighted mean non-inflammatory lesion reduction: BPO 30.9%, clindamycin 32.6%, BPO/salicylic acid 47.8%, BPO/clindamycin 40.3%, placebo 17%).

SUMMARY

Professional guidelines recommend topical therapy as standard of care in acne treatment. The American Acne and Rosacea Society guidelines recommend topical benzoyl peroxide, retinoids, and antibiotics as treatments of choice for pediatrics. The updated American Academy of Dermatology guidelines recommend topical retinoids, benzoyl peroxide, and benzoyl peroxide in combination with either erythromycin or clindamycin as effective acne treatments. They also describe the role of specific topical agents in certain subtypes (e.g., **dapsone for inflammatory acne**, retinoids for comedonal acne, azelaic acid as adjunctive treatment of postinflammatory acne). The Global Alliance to Improve Outcomes in Acne recommends the topical retinoids as the foundation of treatment in all patients with acne except those with the most severe disease. There is no consensus about the relative efficacy of currently available topical retinoids. The concentration and/or vehicle of any particular retinoid may impact tolerability. Combination of a retinoid and antimicrobial such as benzoyl peroxide is the preferred approach for most patients with acne. This combination enhances efficacy and speed of clearing, as the agents target multiple pathophysiological factors and demonstrate broader disease effectiveness. Retinoid monotherapy or combination therapy with benzoyl peroxide should be continued as maintenance treatment due to the potential for bacterial resistance with antibacterials. Combination therapy of topical antibiotics and either benzoyl peroxide or topical retinoids is more effective than either agent used alone.

Benzoyl peroxide has bactericidal, keratolytic, and comedolytic activity. It has been useful as a single agent and in combination with antibiotics or retinoids for acne. Combination therapy of benzoyl peroxide with clindamycin or erythromycin is more effective than either of the individual components

alone. There are many different strengths and formulations available for benzoyl peroxide. It is unknown if there is increased efficacy from higher or lower concentrations of the products, but the incidence of adverse effects may increase with greater concentrations of drug.

Azelaic acid is an effective agent that possesses comedolytic and antibacterial properties, but the comparative data for efficacy are limited. The combination of sulfur and sodium sulfacetamide is another available agent with keratolytic and antibacterial properties, but there is limited data regarding efficacy.

In July 2017, the FDA approved over-the-counter use of Differin 0.1% gel (adapalene) for the treatment of acne. Differin 0.3% gel still requires a prescription.

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